Fig.1A.

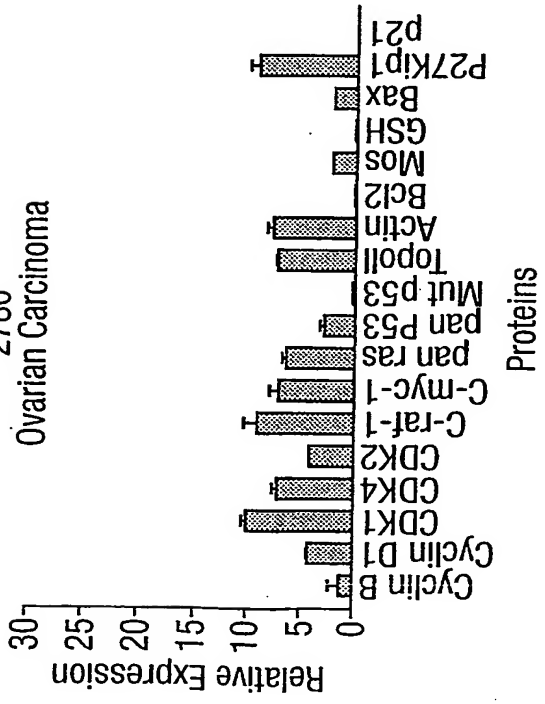


Fig.1B.

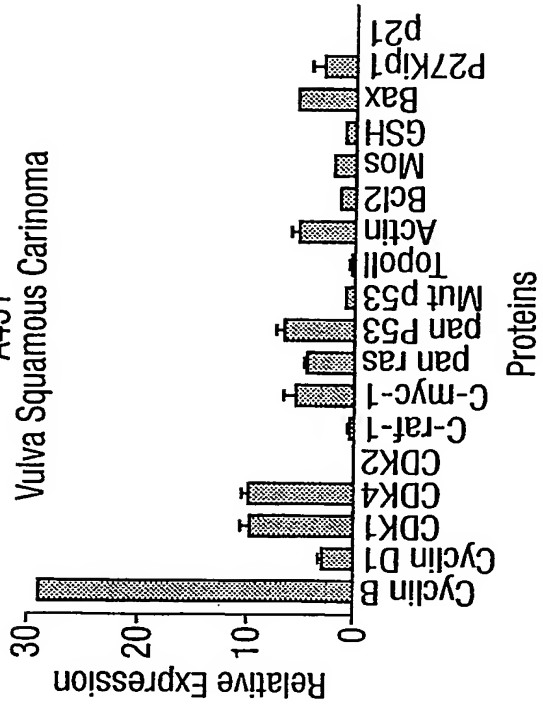


Fig.1C.

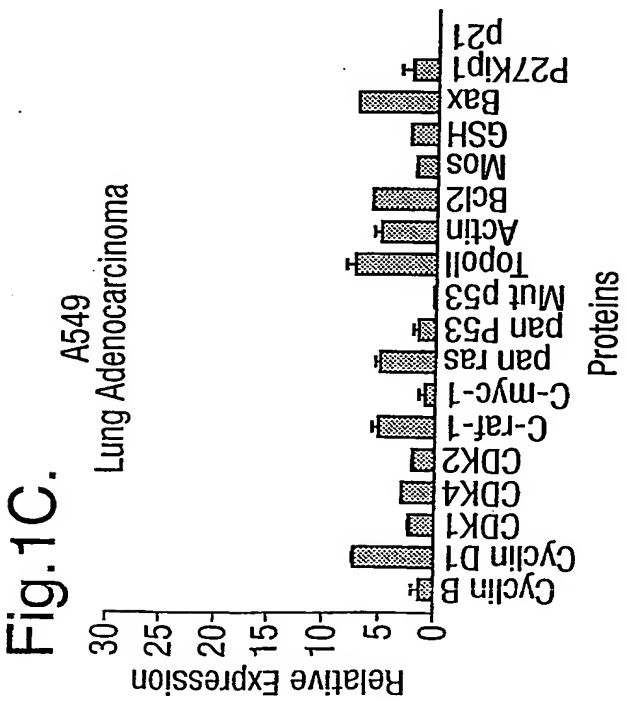
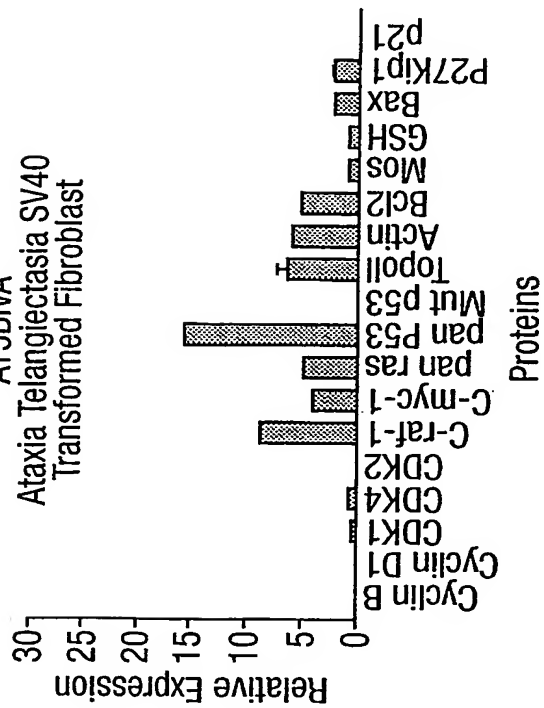


Fig.1D.



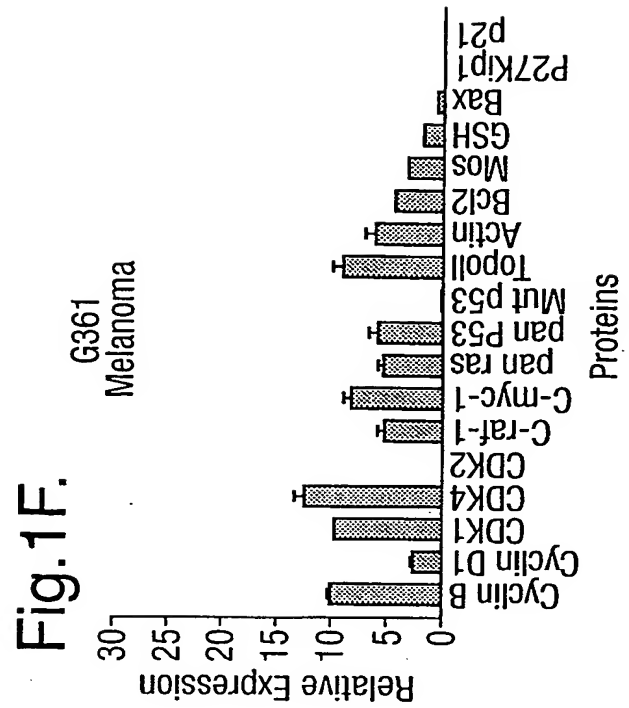


Fig.1F.
G361
Melanoma
Relative Expression
0
5
10
15
20
25
30
Cyclin B
Cyclin D1
CDK1
CDK4
CDK2
C-raf-1
C-myc-1
pan ras
pan P53
Mut p53
TopoII
Actin
Bcl2
Mos
GSH
Bax
P27Kip1
p21
Proteins

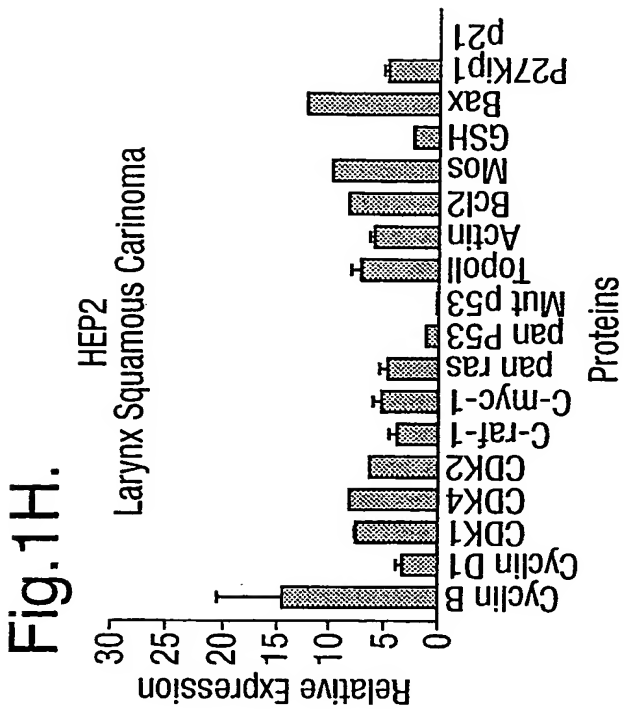


Fig.1H.
HEP2
Larynx Squamous Carinoma
Relative Expression
0
5
10
15
20
25
30
Cyclin B
Cyclin D1
CDK1
CDK4
CDK2
C-raf-1
C-myc-1
pan ras
pan P53
Mut p53
TopoII
Actin
Bcl2
Mos
GSH
Bax
P27Kip1
p21
Proteins

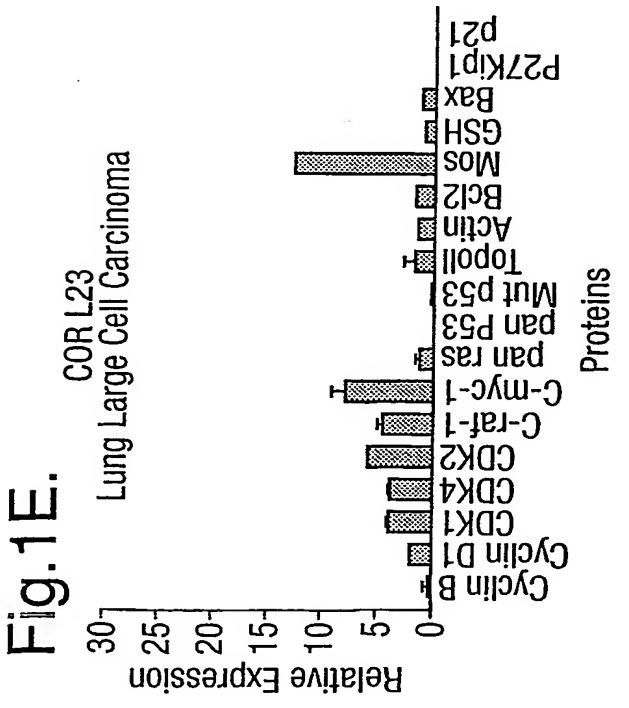


Fig.1E.
COR L23
Lung Large Cell Carcinoma
Relative Expression
0
5
10
15
20
25
30
Cyclin B
Cyclin D1
CDK1
CDK4
CDK2
C-raf-1
C-myc-1
pan ras
pan P53
Mut p53
TopoII
Actin
Bcl2
Mos
GSH
Bax
P27Kip1
p21
Proteins

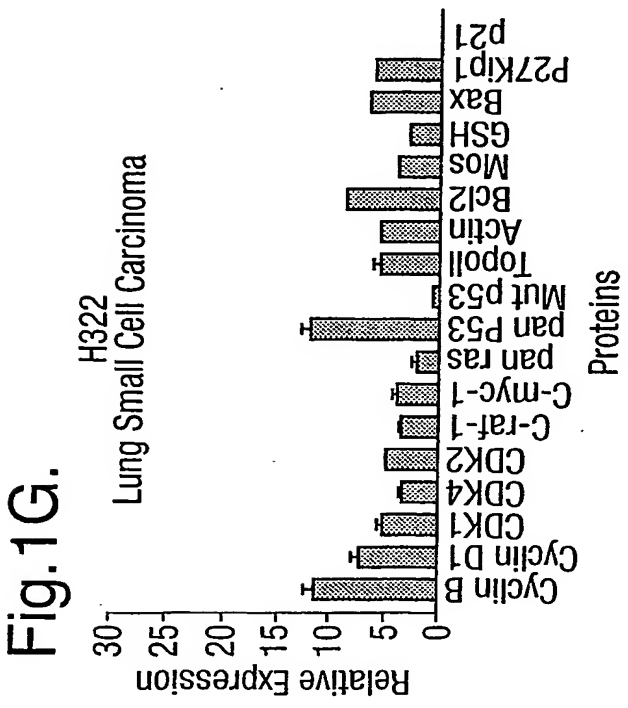


Fig.1G.
H322
Lung Small Cell Carcinoma
Relative Expression
0
5
10
15
20
25
30
Cyclin B
Cyclin D1
CDK1
CDK4
CDK2
C-raf-1
C-myc-1
pan ras
pan P53
Mut p53
TopoII
Actin
Bcl2
Mos
GSH
Bax
P27Kip1
p21
Proteins

Fig.1J.

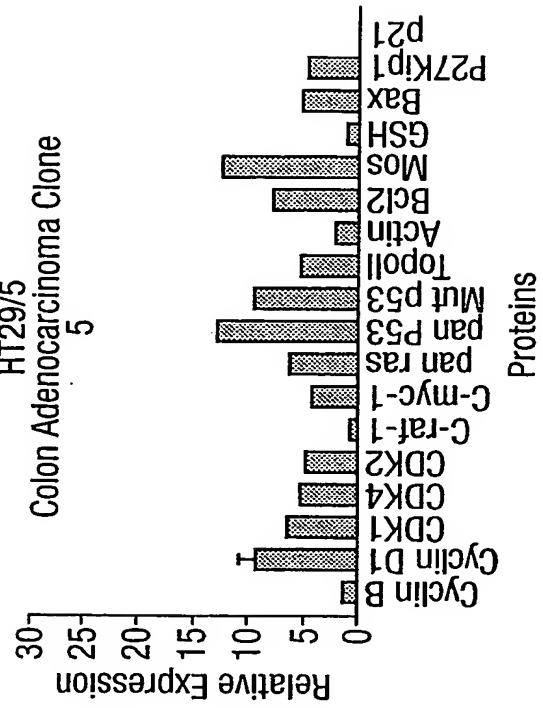


Fig.1L.

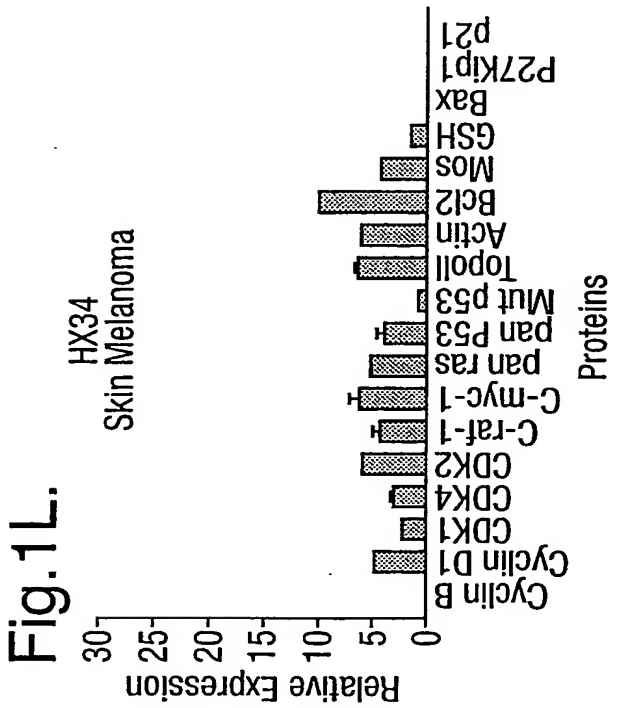


Fig.1I.

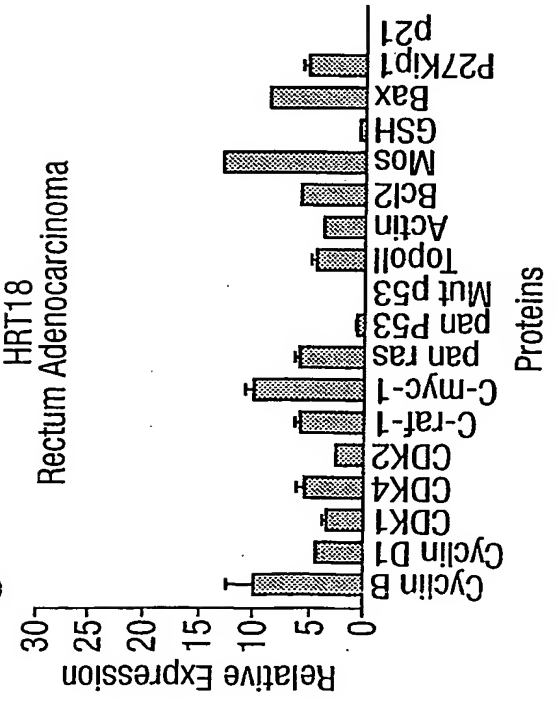


Fig.1K.

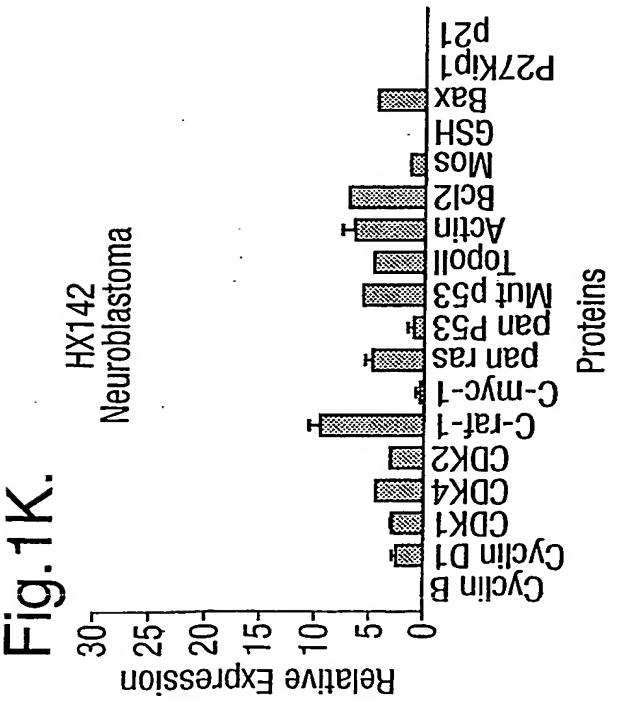


Fig.1N.

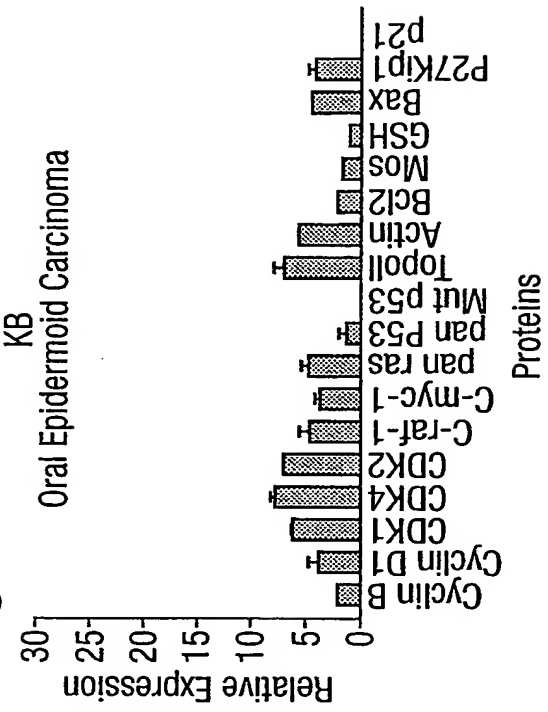


Fig.1P.

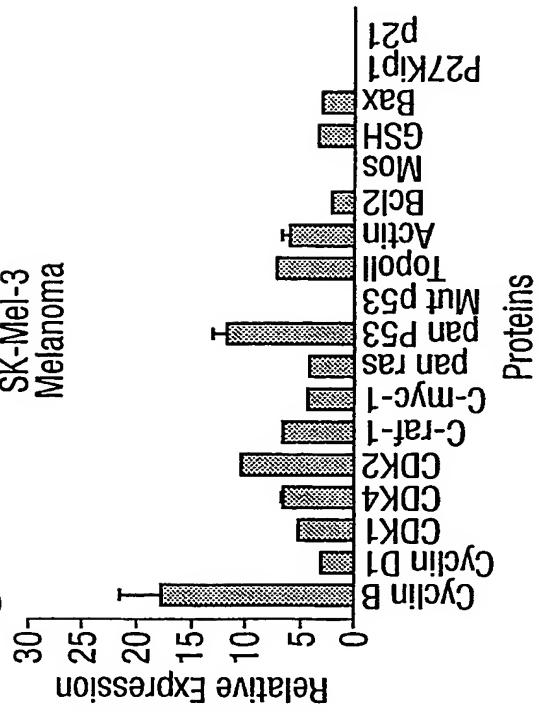


Fig.1M.

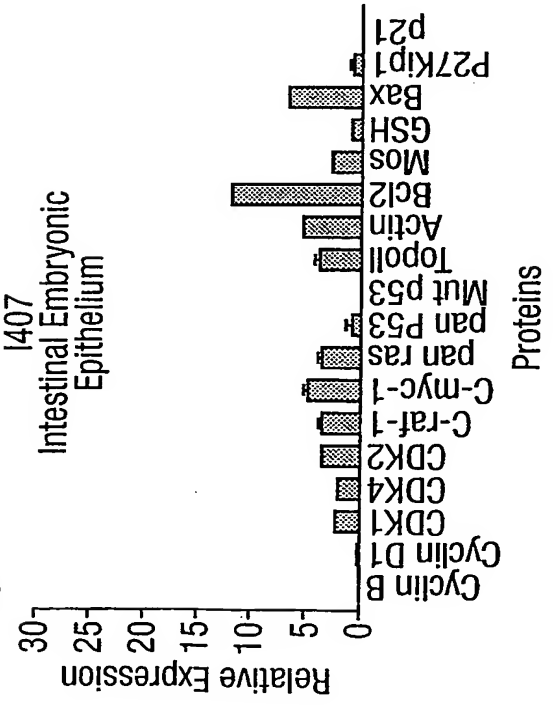
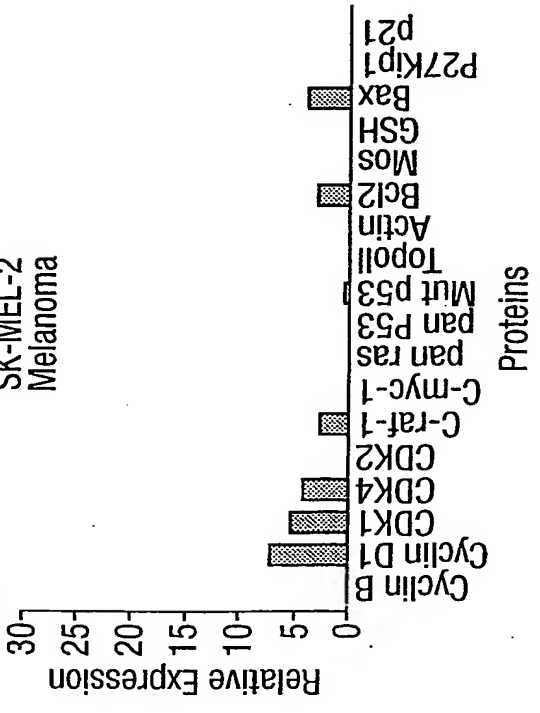


Fig.1O.



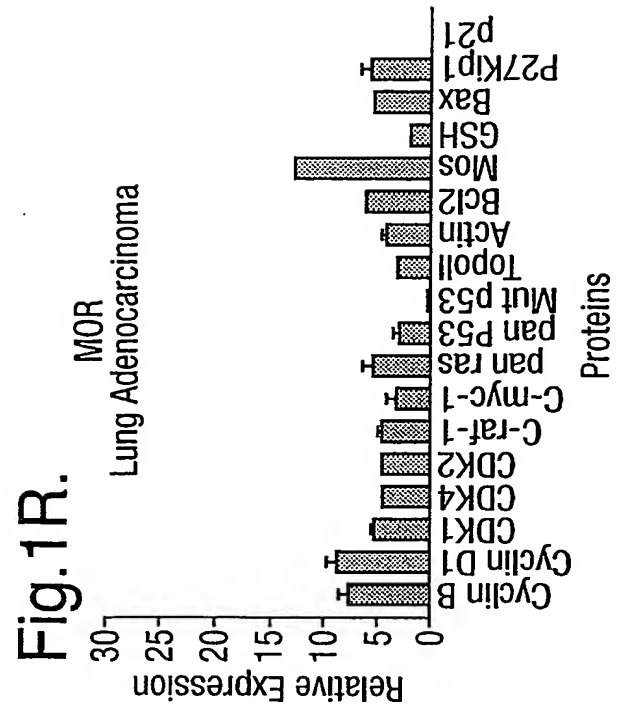


Fig.1R.
MOR
Lung Adenocarcinoma
Relative Expression
0
5
10
15
20
25
30
Cyclin B
Cyclin D1
CDK1
CDK4
CDK2
C-raf-1
C-myc-1
pan ras
pan P53
Mut p53
TopoII
Actin
Bcl2
Mos
GSH
Bax
P27Kip1
p21
Proteins

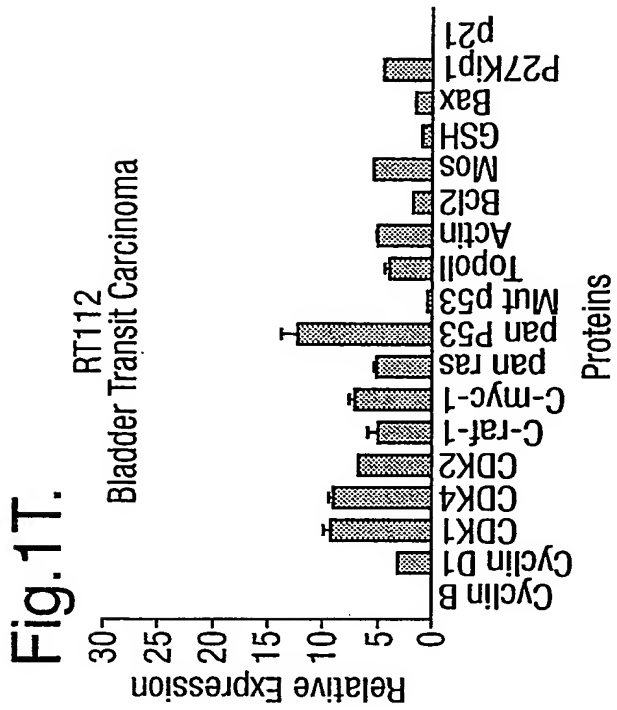


Fig.1T.
RT112
Bladder Transit Carcinoma
Relative Expression
0
5
10
15
20
25
30
Cyclin B
Cyclin D1
CDK1
CDK4
CDK2
C-raf-1
C-myc-1
pan ras
pan P53
Mut p53
TopoII
Actin
Bcl2
Mos
GSH
Bax
P27Kip1
p21
Proteins

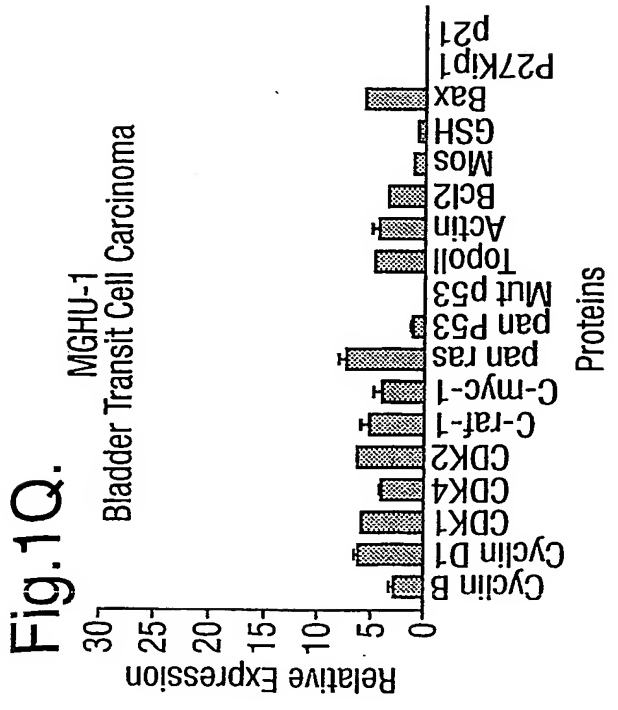


Fig.1Q.
MGHU-1
Bladder Transit Cell Carcinoma
Relative Expression
0
5
10
15
20
25
30
Cyclin B
Cyclin D1
CDK1
CDK4
CDK2
C-raf-1
C-myc-1
pan ras
pan P53
Mut p53
TopoII
Actin
Bcl2
Mos
GSH
Bax
P27Kip1
p21
Proteins

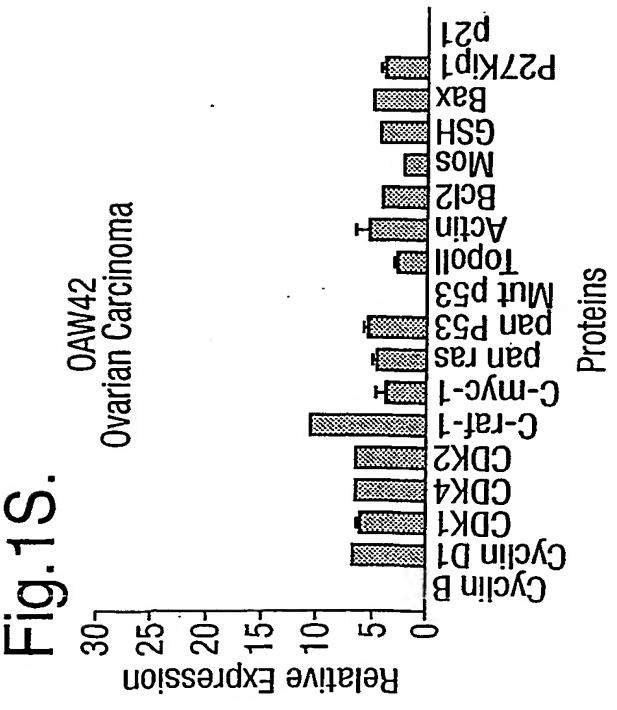


Fig.1S.
OAW42
Ovarian Carcinoma
Relative Expression
0
5
10
15
20
25
30
Cyclin B
Cyclin D1
CDK1
CDK4
CDK2
C-raf-1
C-myc-1
pan ras
pan P53
Mut p53
TopoII
Actin
Bcl2
Mos
GSH
Bax
P27Kip1
p21
Proteins

Fig.2.

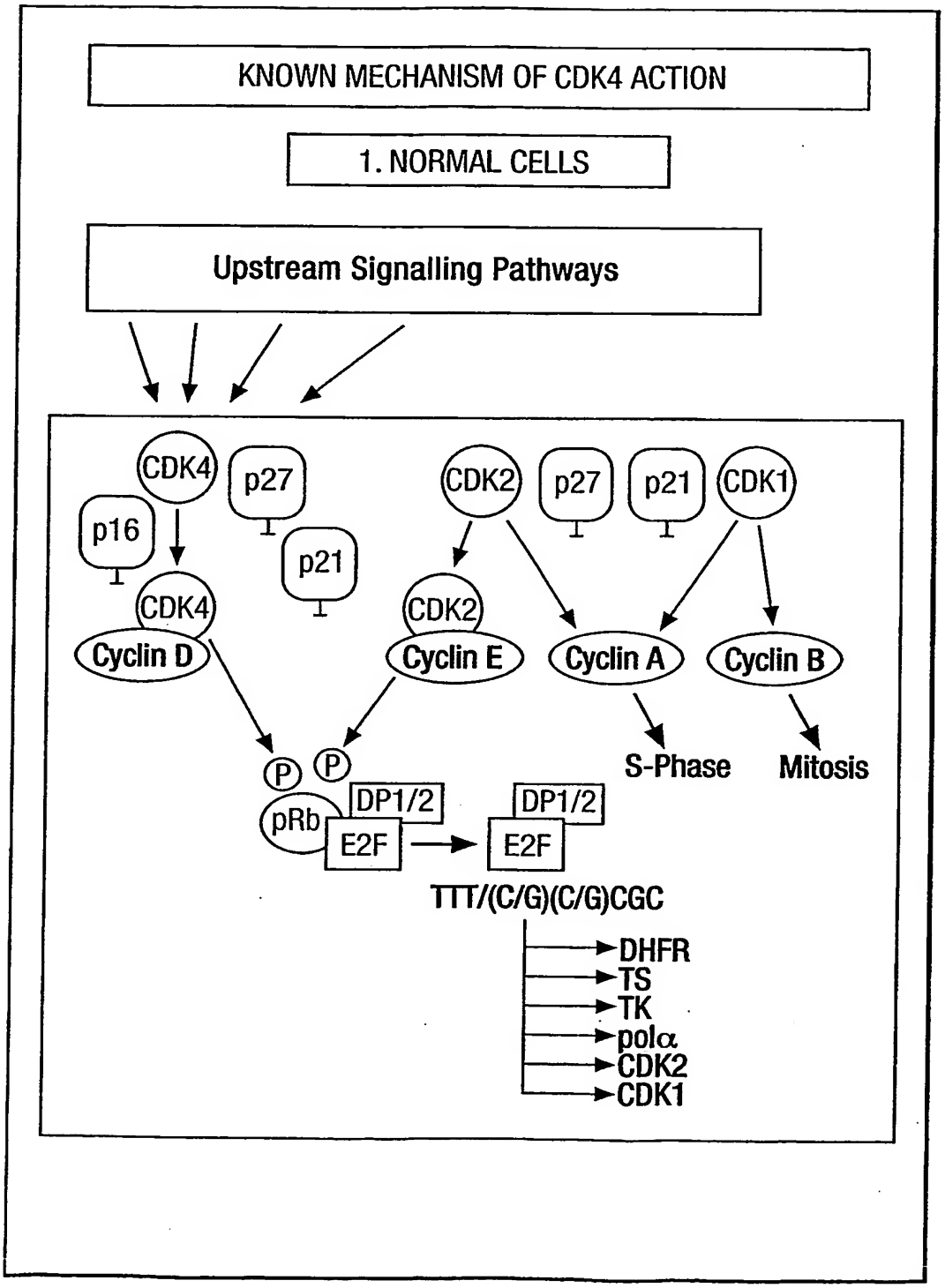

KNOWN MECHANISM OF CDK4 ACTION
1. NORMAL CELLS
Upstream Signalling Pathways
CDK4
p27
p16
p21
CDK4
Cyclin D
CDK2
p27
p21
CDK1
CDK2
Cyclin E
Cyclin A
Cyclin B
S-Phase
Mitosis
P
P
pRb
DP1/2
E2F
DP1/2
E2F
TTT/(C/G)(C/G)CGC
DHFR
TS
TK
polα
CDK2
CDK1

Fig.3.

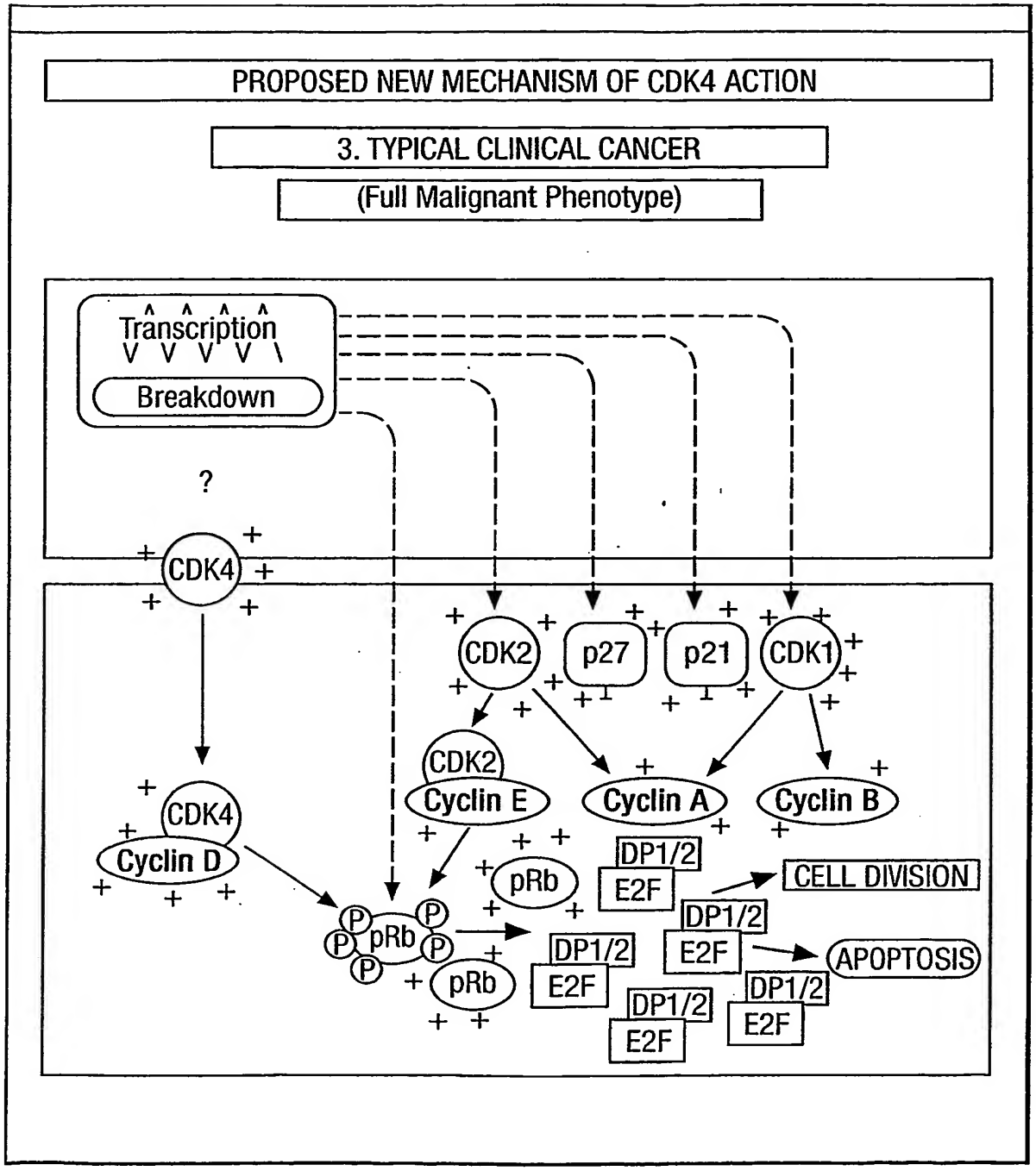
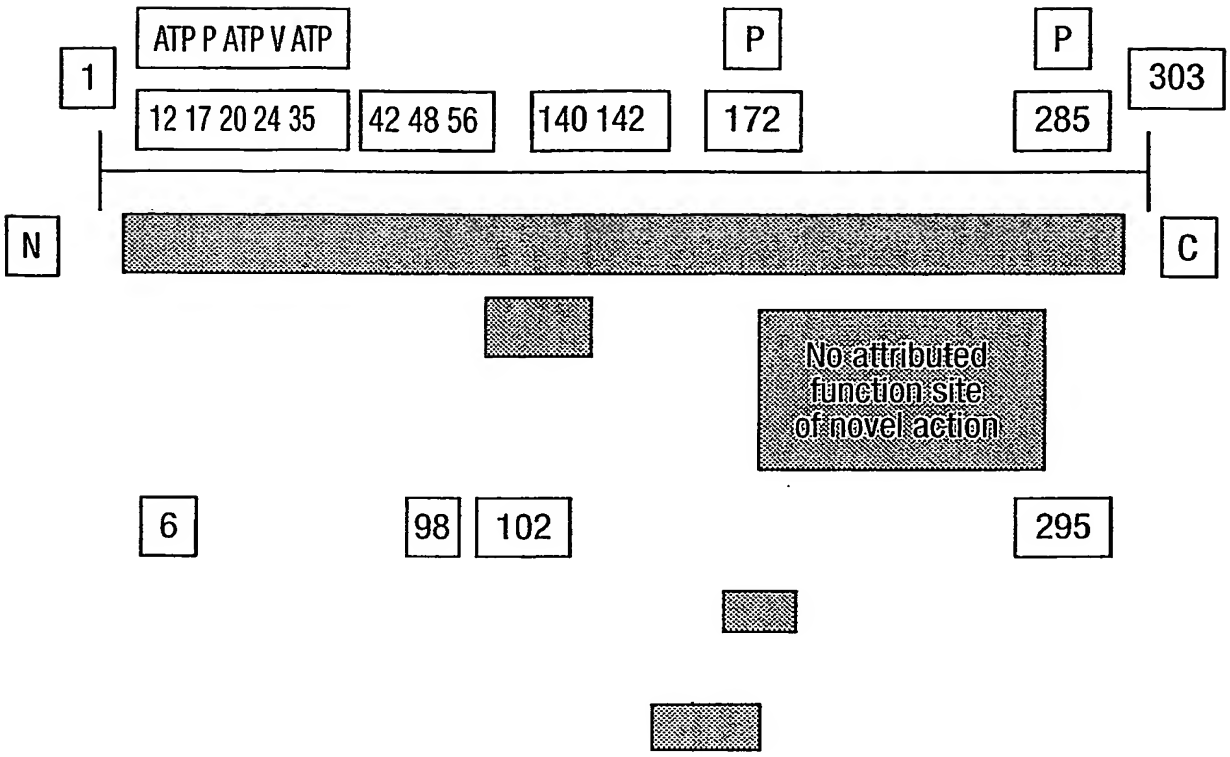

PROPOSED NEW MECHANISM OF CDK4 ACTION
3. TYPICAL CLINICAL CANCER
(Full Malignant Phenotype)
Transcription
Breakdown
?
CDK4
CDK2
p27
p21
CDK1
CDK2
Cyclin E
Cyclin A
Cyclin B
CDK4
Cyclin D
pRb
DP1/2
E2F
CELL DIVISION
APOPTOSIS
P

Fig.4.

CDK4 PROTEIN STRUCTURE (303aa)



6-295	Protein kinase domain
12,20 & 35-ATP binding site	
24(V)-p16^{INK4A} Variant site (R->C in somatic and familial melanoma, generates Arg^{24}->cys, a dominant oncogene resistant to inhibition by p16)	
42,48-polygly domain	
56,140,142-active site	
Gln98, Asp 99 Thr102-p16 binding region	
17-Tyr phosphate binding site	
172-Thr phosphate binding site (necessary for kinase activity)	
285-Ser phosphate binding site	

Fig.5.

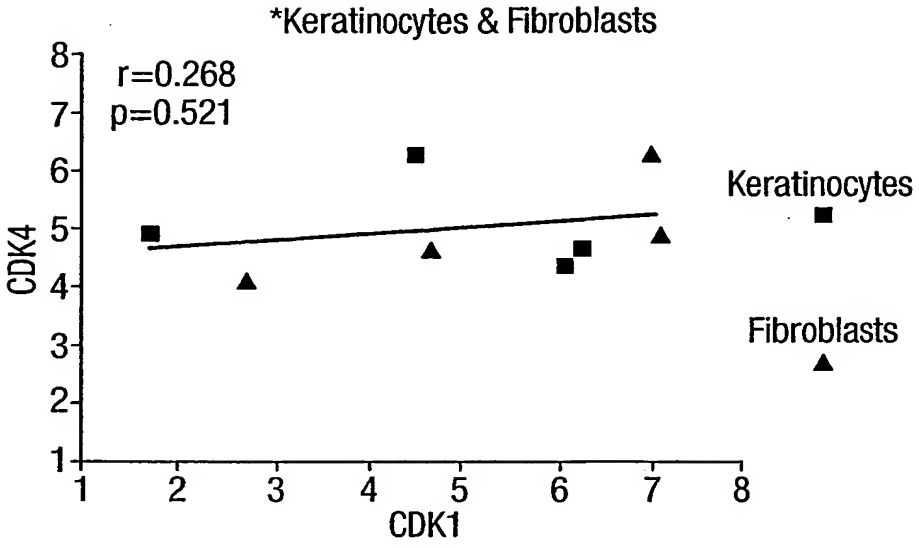

*Keratinocytes & Fibroblasts
r=0.268
p=0.521
Keratinocytes
Fibroblasts
CDK4
CDK1
1
2
3
4
5
6
7
8

Fig.7.

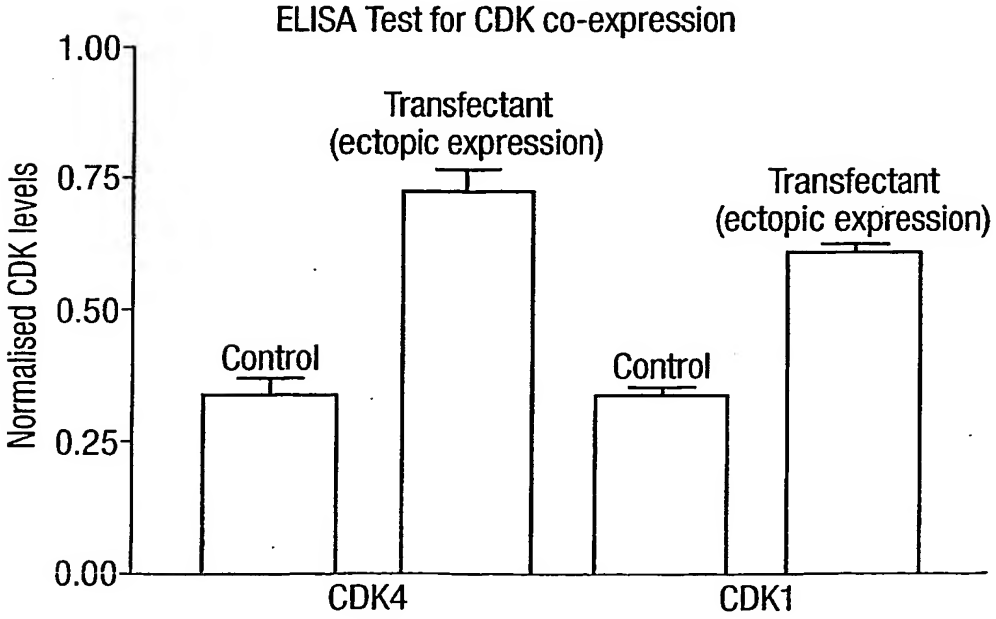
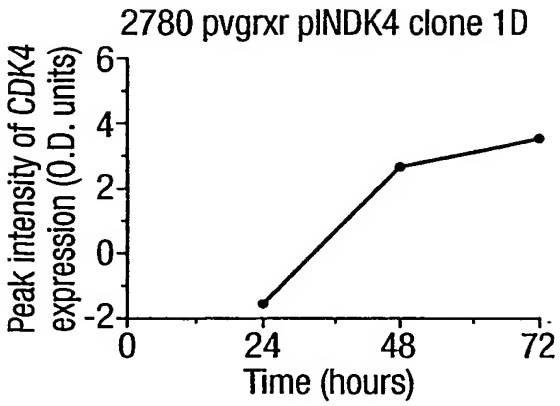
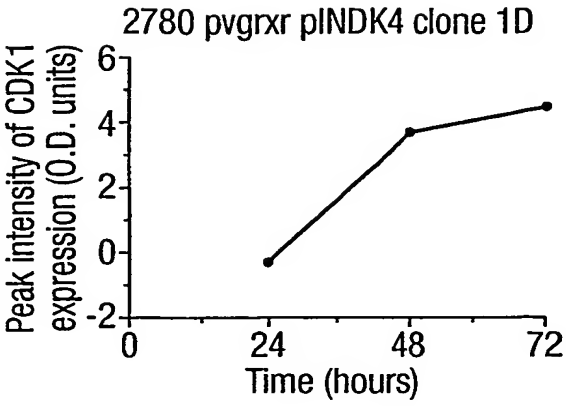
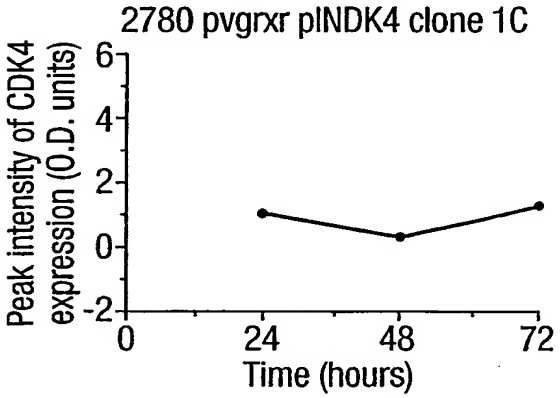
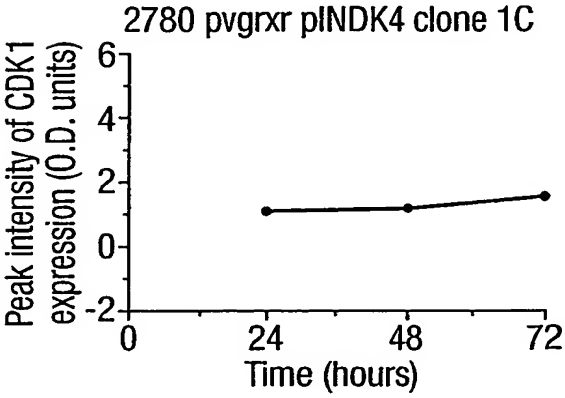

ELISA Test for CDK co-expression
Normalised CDK levels
1.00
0.75
0.50
0.25
0.00
Transfectant
(ectopic expression)
Control
Transfectant
(ectopic expression)
Control
CDK4
CDK1

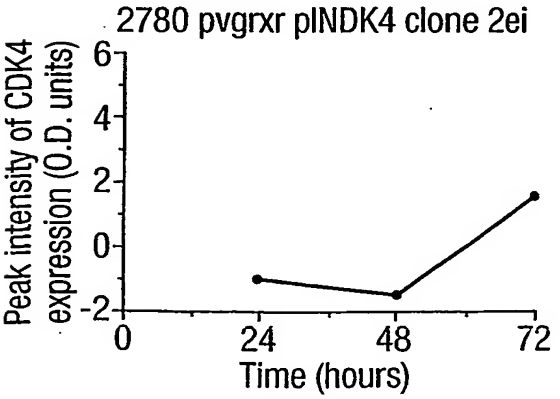
Fig.6.


2780 pvgrxr pINDK4 clone 1D
Peak intensity of CDK4 expression (O.D. units)
6
4
2
0
-2
0
24
48
72
Time (hours)


2780 pvgrxr pINDK4 clone 1D
Peak intensity of CDK1 expression (O.D. units)
6
4
2
0
-2
0
24
48
72
Time (hours)


2780 pvgrxr pINDK4 clone 1C
Peak intensity of CDK4 expression (O.D. units)
6
4
2
0
-2
0
24
48
72
Time (hours)


2780 pvgrxr pINDK4 clone 1C
Peak intensity of CDK1 expression (O.D. units)
6
4
2
0
-2
0
24
48
72
Time (hours)


2780 pvgrxr pINDK4 clone 2ei
Peak intensity of CDK4 expression (O.D. units)
6
4
2
0
-2
0
24
48
72
Time (hours)

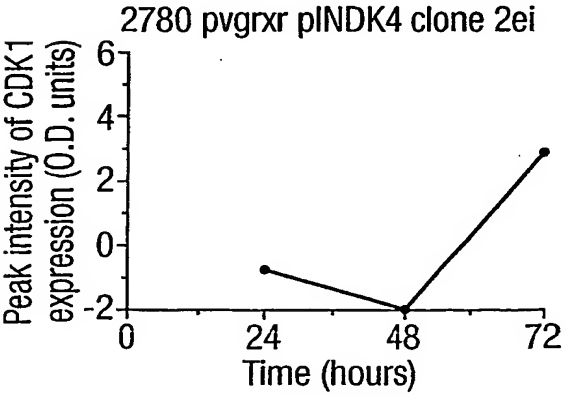

2780 pvgrxr pINDK4 clone 2ei
Peak intensity of CDK1 expression (O.D. units)
6
4
2
0
-2
0
24
48
72
Time (hours)

Fig.8.

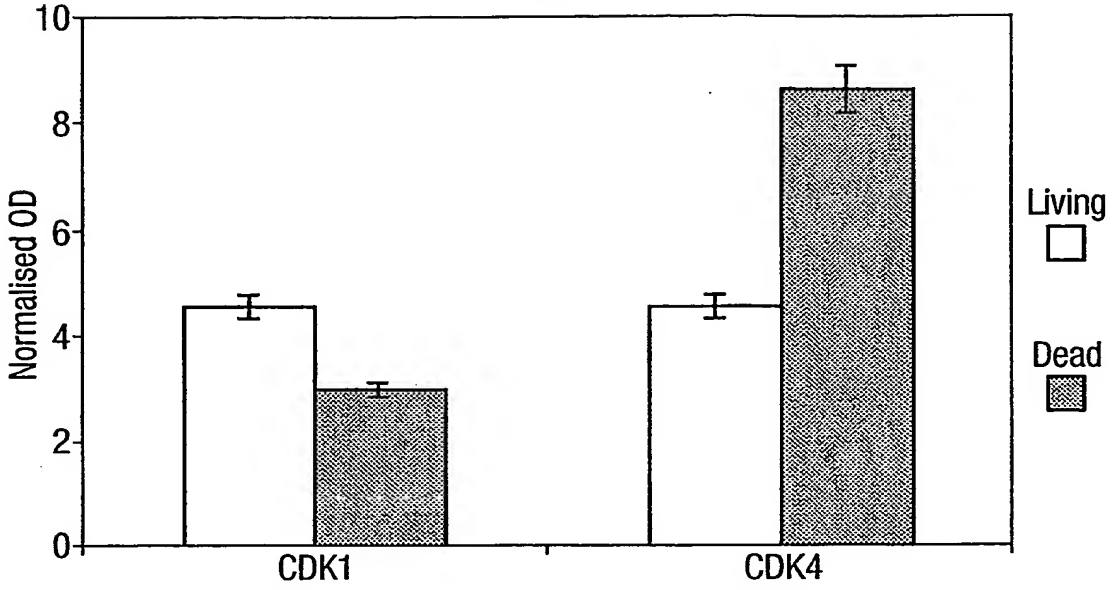


Fig.11A.

Changes in protein expression of Phosphorylated Retinoblastoma Protein p110 [A] and p105 [B] following cell plating

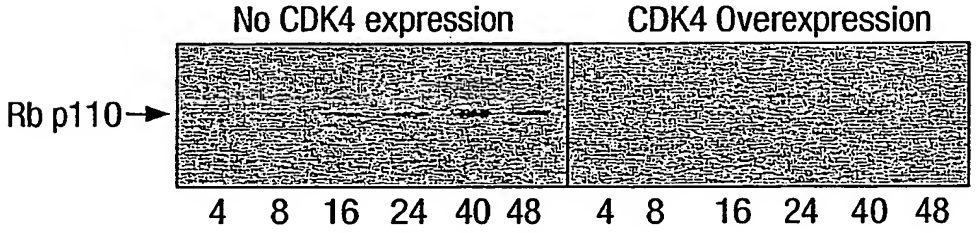
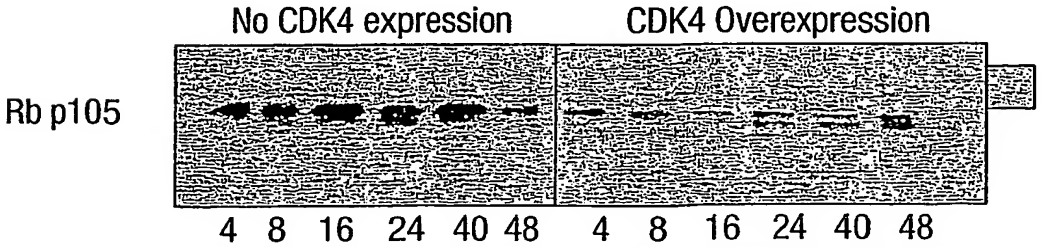


Fig.11B.



Changes in the Phosphorylated Retinoblastoma protein product p110 at times of 4, 8, 16, 24, 40 and 48 hours following cell plating. (pRb retinoblastoma p110 mouse monoclonal antibody IF8. Santa Cruz Biotechnology.CA.USA. pRb retinoblastoma p105 mouse monoclonal antibody NCL-RB-358. Novacastra. Tyneside. UK)

Fig.9.

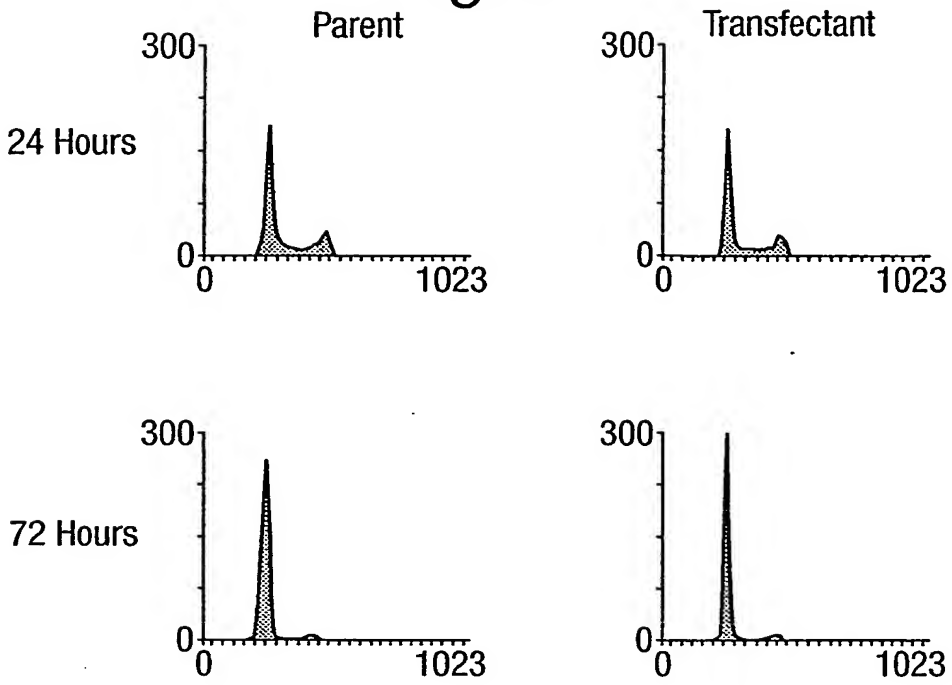


Fig.10A.

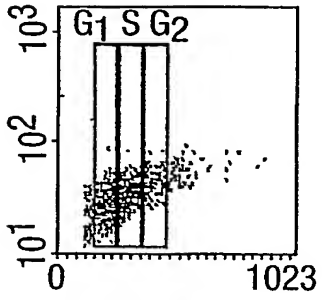


Fig.10B.

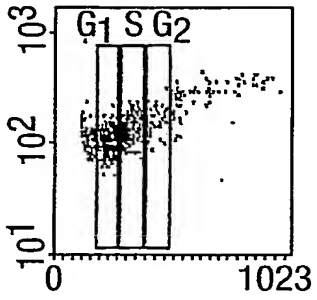


Fig.10C.

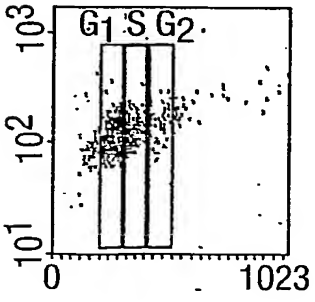


Fig.10D.

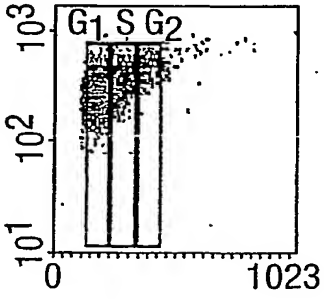
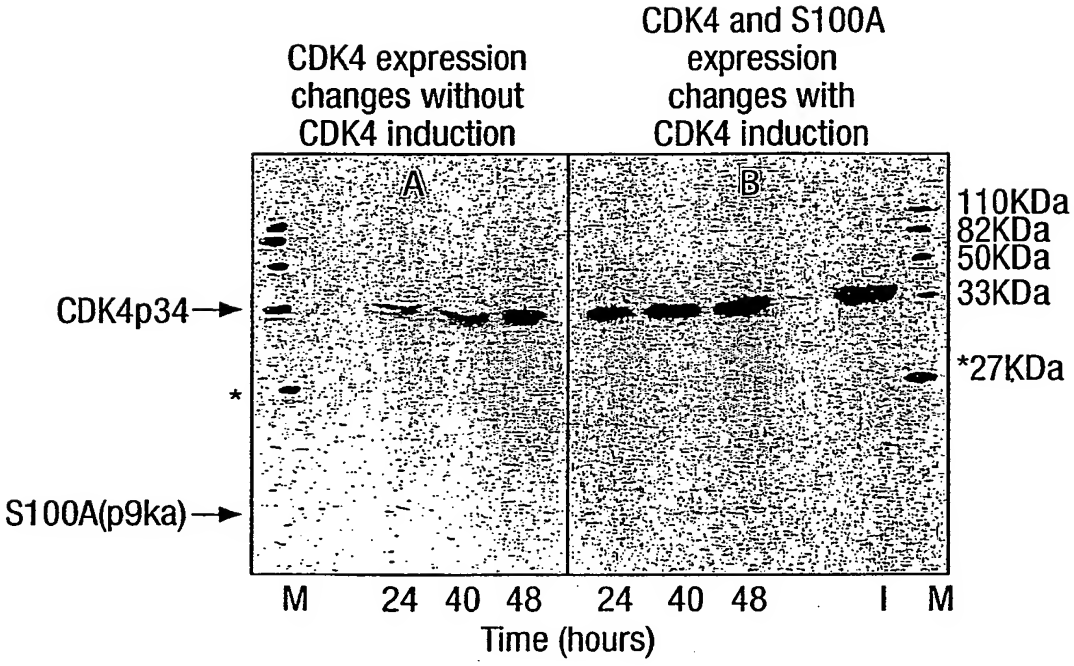


Fig.12.



M=Molecular Weight Markers
I=CDK4 internal standard